Synthesis of Avian-teratogenic Organophosphorus and Methylcarbamate Compounds: Pyrimidine Derivatives.

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Seven pyrimidinyl dialkyl phosphorothionates (**1**, **3**, **10-12**, **14**, **15**), ethyl phenylphosphonothionate (**9**), four dialkyl phosphates (**2**,**5-7**), and dimethylcarbamate (**21**) were synthesized by the reaction of primidinols with dialkyl phosphorothionochloridates, ethyl phenylphosphonothionochloridate, dialkyl phosphorochloridates and dimethylcarbamoyl chloride in 5-99 % yields.

Thermal thiono-thiol conversion of pyrimidinyl *O,O*-diethyl phosphorothionate (**3**) in the synthesis reaction of the diethyl phosphorothionate (**3**) gave pyrimidinyl *O*-ethyl *S*-ethyl phosphorothiolate (**4**).

Oxidation of pyrimidinyl ethyl phenylphosphonothionate (**9**) and dimethyl phosphorothionate by the use of m-chloroperbenzoic acid (MCPBA) gave their corresponding phosphates (**8**, **13**).

Five pyrimidinediyl bis(diethyl phosphorothionates) (**16-20**) were synthesized from pyrimidinediols and two-equivalent amounts of diethyl phosphorothionodichloridate in 6-48% yields.

These products were purified by preparative thin-layer chromatography (tlc) or distillation, and characterized by chemical ionization mass spectrometry and proton NMR spectroscopy.

keywords: teratogen, diazinon, pyrimidinyl dialkyl phosphorothionate, phosphate, pyrimidinediyl bis(diethyl phosphorothionate), dimethylcarbamate, m-chloroperbenzoic acid.

Pyrimidines are important *N*-heterocyclic bases as components of nucleic acid.

One of the derivatives of pyrimidine, diazinon (2-isopropyl-6-methyl-4-pyrimidinyl diethyl phosphorothionate) (**3**) is a potent organophosphorus insecticide[13,14,15] comparable to parathion but showing lower toxicities to warm-blooded animals, and being widely used in Japan.

Several organophosphorus (OP) and methylcarbamate (MC) insecticides are potent teratogens for chicken when injected into hen eggs.[1-3,10,11] Two types of OP- and MC-induced chicken teratogenesis are recognized and termed as type I and type II.[1] Type I teratogenesis gives abnormal feathering and micromelia and is associated with lowering of NAD content in embryo.[1,2] Type II teratogenesis gives

arthrogryposis, wry neck, and rumplessness and is attributable to disruptions of the cholinergic system.[4,1] NAD lowering in Type I teratogenesis results from inhibition of kynurenine formamidase (KFase) (arylformyl-amine amidohydrolase, EC 3.5.1.9) in the pathway of the biosynthesis of NAD.[5]

Primary structure of KFase was recently determined.[18]

Our previous paper[6] described that about 80 OP compounds and carbamates were synthesized or obtained to examine the structural requirements for *in vitro* and *in vivo* mouse liver KFase inhibition and teratogenic potency when injected into hen eggs. Many compounds were newly recognized as potent *in vitro* or *in vivo* KFase inhibitors and as teratogens.[6] Structural requirements for inducing embryonic abnormalities in chickens and KFase inhibition in mouse liver were clarified: The position, size, and branching of *N*-heterocyclic ring substituents in the OP compounds determine their potency and the type of teratogenic signs produced.[6]

Three-dimensional structures of teratogenic OP compounds were analyzed by the use of molecular orbital calculations.[19]

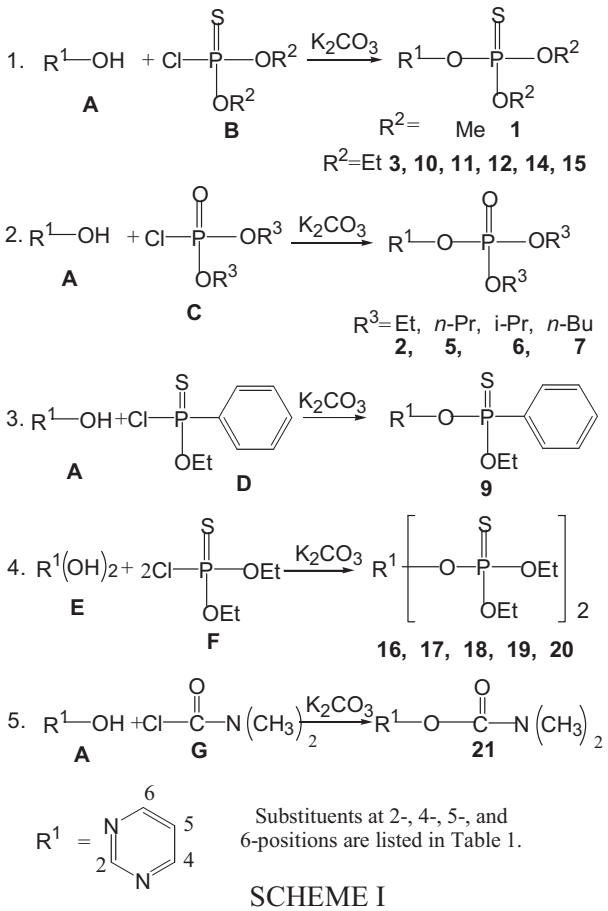
The data on synthesis of several specific compounds were described in detail in the paper 6), while those of the other most compounds tested above were simply described in general because our main interest was in biological activity. The synthesis and spectral data of the OP- and MC-compounds are also very important for the preparation and identification of the compounds. These data of naphthalene OP- and MC-derivatives of were previously published.[21]

The present paper describes the synthesis and spectral data of pyrimidinyl dialkyl phosphorothionates, and dialkyl phosphates, and pyrimidinediyl bis(diethyl phosphoro-thionates), and pyrimidinyl dimethyl-carbamate.

RESULTS AND DISCUSSION

More than 20 organophosphorus and carbamate derivatives of diazinon (**3**) were synthesized for these assays, because diazinon and carbaryl (1-naphthyl monomethyl-carbamate) are very potent chicken-teratogens and kynurenine formamidase inhibitors of mouse liver.[1]

Various substituted pyrimidinyl dialkyl phosphorothionates (**1**, **3**, **10**-**12**, **14**, and **15**) were prepared from the corresponding pyrimidinols (**A**) and dialkyl phosphorothionochloridates (**B**) in the presence of potassium carbonate as an acid scavenger, as shown in SCHEME I-1.



SCHEME I

Solvents used in the reactions were benzene, dimethylformamide (DMF), a mixture of benzene and DMF, and acetonitril, as shown in Table 1. Benzene was used in order to remove water from reaction system by co-distillation as its azeotropic mixture,[13] but the reaction proceeded slowly because of low polarity of this solvent. The other solvents were added or used to increase the polarity of the

reaction solvent. The reaction temperatures are also listed in Table 1.

6-Methyl 2-isopropyl 4-hydroxypyrimidine (**A**) were allowed to react with equivalent amounts of dimethyl and diethyl phosphorothionochloridates (**B**) to give their dimethyl and diethyl phosphorothionates (**1** and **3**) in the yields 19% and 19%, after purification by preparative tlc with solvent D and E, respectively, as shown in Table 1.

Compound **1** gave the proper M+1 peak in ci/ms, and doublet of methoxy group coupled with phosphorus atom (δ 3.96, J=14.2 Hz) and doublet (δ 1.32, J=6.9 Hz) for dimethyl group coupled with one proton (δ 3.13, multiplet) of 2-isopropyl group, singlet (δ 2.49) for 6-methyl group and singlet (δ 6.65) for 5-hydrogen in proton NMR spectra as shown in Table 1. These results showed the prepared compound was **1**.

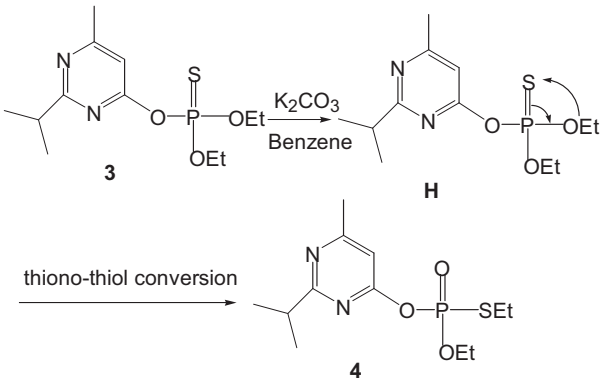
On the other hand, compound **3** gave the proper M+1 peak in ci/ms and triplet (δ 1.39, J= 7.1 Hz) with fine structure of methyl group and double quartet (δ 4.36, $J_{P\text{-}CH}$=9.6 Hz and $J_{CH\text{-}CH3}$=7.1 Hz) of methylene group of ethoxy group and about the same data for protons of the substituted pyrimidine in NMR spectra as those for **1**, as shown in Table 1. These spectral data shows the structure is the desired one of **3**.

6-Methyl 2-isopropyl 4-hydroxypyrimidinyl ethyl phenylphosphonothionate (**9**) was synthesizedby the use of ethyl phenylphosphonothionochloridate as phosphorylating agent, as shown in Scheme I-3.

NMR spectrum of **9** showed the unique figure that the two methyl groups of 2-isopropyl group gave two different peaks (δ 1.17 (doublet, J=6.8 Hz) and 1.23 (doublet, J=6.8 Hz)), respectively, as shown in Table 1.

6-Methyl 2-isopropyl 4-hydroxypyrimidinyl *O*-ethyl *S*-ethyl phosphorothiolate (**4**) was isolated by the preparative tlc from the reaction mixtures for the synthesis of **3**, and identified by the use of ci/ms and proton NMR spectroscopy which showed clear P-S-CH_2 chemical shift value (δ 3.18), as shown in Table 1.

The mechanism for the formation of **4** is proposed to be the thermal thiono-thiol conversion (**H**) of **3** to **4**, as shown in SCHEME II.



SCHEME II

Gysin and Margot previously reported the existence of the by-product **4**, isodiazinon, in the reaction system for diazinon synthesis.[13]

With regards to thiono-thiol conversion of organophosphorus compounds, we reported previously the synthesis of 2-methylthio-4*H*-1,3,2-benzodioxaphosphorin 2-oxide (MTBO)[16] from thiono isomer, salithion,[12] a practical insecticide.

6-Methyl 2-isopropyl 4-hydroxypyrimidinyl dialkyl phosphates (**2**, **5**, **6** and **7**) were also synthesized by the use of dialkyl phosphorochloridate (**C**) by the similar procedures as those used in the preparation of **3** except that the reactions were carried out at room temperatures, as shown in SCHEME I-2 and Table 1. These compounds were purified by preparative tlc with the solvent listed in Table 1 to give in 13-43% yield. These compounds gave proper ci/ms M+1 peaks and all its NMR peaks are assigned to the structures of **2**, **5**, **6** and **7**, as shown in Table 1.

For preparation of phosphate (oxon) (**J**), oxidation of phosphorothionate (thion) (**I**) with m-chloroperbenzoic acid (MCPBA) was also applied according to the previously reported procedure.[17]

Thions (**I**), **9** and 2-ethyl 6-ethoxy 4-pyrimidinyl dimethyl phosphorothionate

Table 1 (Left)

 Substituent						Synthesis	Isolated	TLC		CI/MS
Compound		2	4	5	6	Reaction	Yield	Solvent	Rf	[M+1]
No.	No. *1					Condition	(%)	System	value	
1	15	i-Pr	$OP(S)(OMe)_2$	H	Me	K_2CO_3/DMF (60°C, 2 hr)	19	D	0.74	277
2	16	i-Pr	$OP(O)(OEt)_2$	H	Me	K_2CO_3/Benzene (23°C, 42 hr)	13	D	0.34	289
3	17	i-Pr	$OP(S)(OEt)_2$	H	Me	K_2CO_3/Benzene (60°C, 5 hr)	19	E	0.47	305
4	18	i-Pr	OP(O)(OEt)(SEt)	H	Me	K_2CO_3/Benzene (60°C, 5 hr)	5	E	0.26	305
5	19	i-Pr	$OP(O)(O\text{-}n\text{-}Pr)_2$	H	Me	K_2CO_3/Benzene (70°C, 14 hr)	19	E	0.28	317
6	20	i-Pr	$OP(O)(O\text{-}i\text{-}Pr)_2$	H	Me	K_2CO_3/Benzene (23°C, 45 hr)	43	D	0.37	317
7	21	i-Pr	$OP(O)(O\text{-}n\text{-}Bu)_2$	H	Me	K_2CO_3/Benzene (23°C, 43 hr)	24	D	0.49	345
8	22	i-Pr	OP(O)(OEt)Ph	H	Me	MCPBA/CH_2Cl_2 (23°C, 2 hr)	25	D*2 C E	0.30 0.19 0.16	*4
9	23	i-Pr	OP(S)(OEt)Ph	H	Me	K_2CO_3/Benzene (70°C, 4 days)	67	E*2 C D	0.39 0.77 0.74	337
10	24	H	$OP(S)(OEt)_2$	H	H	K_2CO_3/Benzene (60°C, 37 hr)	31	E	0.25	249
11	25	Me	$OP(S)(OEt)_2$	H	Me	K_2CO_3/(Benzene)DMF (60°C, 3 hr)	58	C	0.51	277
12	26	*n*-Pr	$OP(S)(OEt)_2$	H	Me	K_2CO_3/(Benzene)DMF (65°C, 4.8 days)	68	E	0.34	305
13	27	Et	$OP(O)(OMe)_2$	H	OEt	MCPBA/CH_2Cl_2 (23°C, 2 hr)	24	E*2 D C	0.15 0.47 0.40	277
14	29	Et	$OP(S)(OEt)_2$	H	OEt	K_2CO_3/CH_3CN (50°C, 3 hr)	58	A*2 E	0.46 0.44	321
15	36	$OP(S)(OEt)_2$	H	H	Me	K_2CO_3/(Benzene)DMF (25°C, 2hr+65°C, 0.5hr)	56	E	0.24	263
16	32	H	$OP(S)(OEt)_2$	H	$OP(S)(OEt)_2$	K_2CO_3/(Benzene)DMF (65°C, 3 hr)	9	E*2 A	0.28 0.20	417
17	33	Me	$OP(S)(OEt)_2$	H	$OP(S)(OEt)_2$	K_2CO_3/Benzene (70°C, 3.8 days)	48	E	0.32	431
18	34	$OP(S)(OEt)_2$	$OP(S)(OEt)_2$	H	H	K_2CO_3/(Benzene)DMF (65°C, 3 hr)	20	E*2 A	0.20 0.23	417
19	35	$OP(S)(OEt)_2$	$OP(S)(OEt)_2$	H	Me	K_2CO_3/(Benzene)DMF (65°C, 3 hr)	6	E	0.23	431
20	57	$OP(S)(OEt)_2$	$OP(S)(OEt)_2$	Me	H	K_2CO_3/(Benzene)DMF (65°C, 3 hr)	14	E*2 A	0.24 0.28	431
21	37	i-Pr	$OC(O)NMe_2$	H	Me	K_2CO_3/DMF (60°C, 1 hr)	99*3	B	0.36	224

*1 Compound No in the reference 6). *2 Solvent system used for purification of the desired compound.

*3 b.p. 82°C/0.125 mmHg. *4 [M+1] peak was not observed.

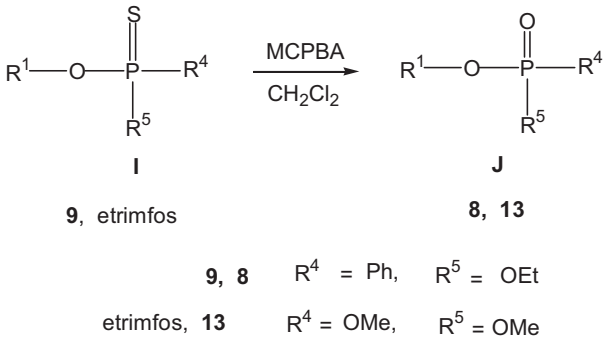
Tabel 1 (Right)

NMR*5, *6							
2		4		5		6	
$CH(\mathbf{CH_3})_2$	1.32 (d, 6.9)	$P(OCH_3)_2$	3.96 (d, 14.2)	H	6.65 (s)	CH_3	2.49 (s)
$\mathbf{CH}(CH_3)_2$	3.13 (m)						
$CH(\mathbf{CH_3})_2$	1.32 (d, 6.8)	$P(OCH_2\mathbf{CH_3})_2$	1.39 (t (f), 7.1)	H	6.72 (s)	CH_3	2.49 (s)
$\mathbf{CH}(CH_3)_2$	3.12 (m)	$P(O\mathbf{CH_2}CH_3)_2$	4.34 (m)				
$CH(\mathbf{CH_3})_2$	1.31 (d, 6.8)	$P(OCH_2\mathbf{CH_3})_2$	1.39 (t (f), 7.1)	H	6.66 (s)	CH_3	2.49 (s)
$\mathbf{CH}(CH_3)_2$	3.08 (m)	$P(O\mathbf{CH_2}CH_3)_2$	4.36 (dq, 9.6, 7.1)				
		$POCH_2\mathbf{CH_3}$	1.47 (m)				
$CH(\mathbf{CH_3})_2$	1.36 (d, 7.2)	$PSCH_2\mathbf{CH_3}$	1.47 (m)	H	6.97 (s)	CH_3	2.58 (s)
$\mathbf{CH}(CH_3)_2$	3.18 (m)	$PS\mathbf{CH_2}CH_3$	3.18 (m)				
		$PO\mathbf{CH_2}CH_3$	4.46 (m)				
		$P(OCH_2CH_2\mathbf{CH_3})_2$	0.98 (t, 7.3)				
$CH(\mathbf{CH_3})_2$	1.31 (d, 6.8)	$P(OCH_2\mathbf{CH_2}CH_3)_2$	1.76 (m)	H	6.72 (s)	CH_3	2.49 (s)
$\mathbf{CH}(CH_3)_2$	3.12 (m)	$P(O\mathbf{CH_2}CH_2CH_3)_2$	4.22 (m)				
$CH(\mathbf{CH_3})_2$	1.35 (m)	$P[OCH(\mathbf{CH_3})_2]_2$	1.35 (m)	H	6.73 (s)	CH_3	2.48 (s)
$\mathbf{CH}(CH_3)_2$	3.12 (m)	$P[O\mathbf{CH}(CH_3)_2]_2$	4.90 (m)				
		$P(OCH_2CH_2CH_2\mathbf{CH_3})_2$	0.94 (m)				
$CH(\mathbf{CH_3})_2$	1.31 (d, 6.9)	$P(OCH_2\mathbf{CH_2}CH_2CH_3)_2$	1.60 (m)	H	6.72 (s)	CH_3	2.48 (s)
$\mathbf{CH}(CH_3)_2$	3.12 (m)	$P(O\mathbf{CH_2}CH_2CH_2CH_3)_2$	4.26 (m)				
		$POCH_2\mathbf{CH_3}$	1.41 (t, 7.2)				
$CH(\mathbf{CH_3})_2$	1.20 (m)	$PO\mathbf{CH_2}CH_3$	4.40 (m)	H	6.69 (s)	CH_3	2.44 (s)
$\mathbf{CH}(CH_3)_2$	3.03 (m)	P-Ph	7.50 (m, 3H) 7.95 (m, 2H)				
$CH\mathbf{CH_3}$	1.17 (d, 6.8)	$POCH_2\mathbf{CH_3}$	1.41 (t, 7.1)				
$CH\mathbf{CH_3}$	1.23 (d, 6.8)	$PO\mathbf{CH_2}CH_3$	4.46 (m)	H	6.61 (s)	CH_3	2.45 (s)
$\mathbf{CH}(CH_3)_2$	3.00 (m)	P-Ph	7.49 (m, 3H) 8.04 (m, 2H)				
H	8.95 (s)	$P(OCH_2\mathbf{CH_3})_2$	1.40 (t (f), 7.1)	H	7.05 (d, 5.6)	H	8.69 (d, 5.7)
		$P(O\mathbf{CH_2}CH_3)_2$	4.36 (dq, 9.9, 7.1)				
CH_3	2.63 (s)	$P(OCH_2\mathbf{CH_3})_2$	1.40 (t (f), 7.1)	H	6.71 (s)	CH_3	2.49 (s)
		$P(O\mathbf{CH_2}CH_3)_2$	4.35 (dq, 9.7, 7.1)				
$CH_2CH_2\mathbf{CH_3}$	0.98 (t, 7.2)						
$CH_2\mathbf{CH_2}CH_3$	1.83 (m)	$P(OCH_2\mathbf{CH_3})_2$	1.39 (t (f), 7.1)	H	6.69 (s)	CH_3	2.49 (s)
$\mathbf{CH_2}CH_2CH_3$	2.84 (t, 7.5)	$P(O\mathbf{CH_2}CH_3)_2$	4.35 (dq, 9.8, 7.1)				
$CH_2\mathbf{CH_3}$	1.31 (t, 7.2)	$P(OCH_3)_2$	3.95 (d, 10.8)	H	6.18 (s)	$OCH_2\mathbf{CH_3}$	1.38 (t, 7.2)
$\mathbf{CH_2}CH_3$	2.82 (q, 7.2)					$O\mathbf{CH_2}CH_3$	4.42 (q, 7.2)
$CH_2\mathbf{CH_3}$	1.31 (m)	$P(OCH_2\mathbf{CH_3})_2$	1.38 (m)	H	6.19 (s)	$OCH_2\mathbf{CH_3}$	1.38 (m)
$\mathbf{CH_2}CH_3$	2.80 (m)	$P(O\mathbf{CH_2}CH_3)_2$	4.35 (m)			$O\mathbf{CH_2}CH_3$	4.35 (m)
$P(OCH_2\mathbf{CH_3})_2$	1.40 (t, 7.1)	H	8.47 (d, 4.6)	H	7.02 (d, 5.0)	CH_3	2.52 (s)
$P(O\mathbf{CH_2}CH_3)_2$	4.39 (m)						
H	8.68 (s)	$P(OCH_2\mathbf{CH_3})_2$	1.40 (t, 7.1)	H	6.71 (s)	$P(OCH_2\mathbf{CH_3})_2$	1.40 (t, 7.1)
		$P(O\mathbf{CH_2}CH_3)_2$	4.35 (dq, 9.9, 7.0)			$P(O\mathbf{CH_2}CH_3)_2$	4.35 (dq, 9.9, 7.0)
CH_3	2.60 (s)	$P(OCH_2\mathbf{CH_3})_2$	1.39 (t, 7.1)	H	6.58 (s)	$P(OCH_2\mathbf{CH_3})_2$	1.39 (t, 7.1)
		$P(O\mathbf{CH_2}CH_3)_2$	4.35 (dq, 10.7, 7.1)			$P(O\mathbf{CH_2}CH_3)_2$	4.35 (dq, 10.7, 7.1)
$P(OCH_2\mathbf{CH_3})_2$	1.40 (t, 7.1)	$P(OCH_2\mathbf{CH_3})_2$	1.40 (t, 7.1)	H	6.91 (d, 5.5)	H	8.55 (d, 5.5)
$P(O\mathbf{CH_2}CH_3)_2$	4.37 (m)	$P(O\mathbf{CH_2}CH_3)_2$	4.37 (m)				
$P(OCH_2\mathbf{CH_3})_2$	1.39 (t, 7.1)	$P(OCH_2\mathbf{CH_3})_2$	1.39 (t, 7.1)	H	6.74 (s)	CH_3	2.50 (s)
$P(O\mathbf{CH_2}CH_3)_2$	4.36 (m)	$P(O\mathbf{CH_2}CH_3)_2$	4.36 (m)				
$P(OCH_2\mathbf{CH_3})_2$	1.40 (t, 7.0)	$P(OCH_2\mathbf{CH_3})_2$	1.40 (t, 7.0)	CH_3	2.20 (s)	H	8.36 (s)
$P(O\mathbf{CH_2}CH_3)_2$	4.38 (m)	$P(O\mathbf{CH_2}CH_3)_2$	4.38 (m)				
$CH(\mathbf{CH_3})_2$	1.33 (d, 6.8)	$C(O)N(CH_3)_2$	3.02 (s), 3.11 (s)	H	6.84 (s)	CH_3	2.50 (s)
$\mathbf{CH}(CH_3)_2$	3.1 (m)						

*5 s: singlet; d: doublet; dq: double quartet; t: triplet; t(f): triplet with fine structure; m: multiplet; q: quartet.

*6 Numerical values are chemical shifts: δ (ppm); and those in parentheses are coupling constants: J (Hz).

(etrimfos), were oxidized by MCPBA in the methylene chloride solution to give their oxon (**J**) (**8** and **13**), respectively, as shown in SCHEME III and Table 1.



SCHEME III

Substituted pyrimidinediyl bis(diethyl phosphorothionates) (**16**-**20**) were synthesized from primidinediol (**E**) and two-equivalent amounts of diethyl phosphorothionodichloridate (**F**), in 6-48% yields, as shown in SCHEME I-4 and Table 1, where starting pyrimidinediols (**E**) of **18** and **20** were uracil and thymine, important component bases of nucleic acids, RNA and DNA, respectively.

Pyrimidinyl dimethylcarbamate (**21**) was synthesized for biological assay because compound **21** has both carbamoyl group of carbaryl and pyrimidinyl group of diazinon.

Synthesis of this compound (**21**) was carried out by the use of a small modification of the previously reported procedure.[8] Dimethylformamide (DMF) was a good solvent and catalyst in the reaction. Equivalent amount of dimethylcarbamoyl chloride (**G**) was allowed to react with 6-methyl 2-isopropyl 4-hydroxypyrimidine (**A**) in the presence of potassium carbonate to give **21** in 99% yield, as shown in SCHEME I-5 and Table 1. Tlc showed the quantitative yield of the desired product positive in ninhydrin test. Distillation *in vacuo* was effective to give a colorless liquid. Rf values of the compound **21** and the starting material are 0.36 and 0.02 in solvent B, respectively.

Ci/ms data gave the proper M+1 peak, and NMR spectra showed two sharp singlets for dimethylcarbamoyl group (δ 3.02 and 3.11) and the proper spectral data for the substituted pyrimidinyl group (Table 1), which showed the prepared compound was **21**.

Thus, pyrimidinyl dialkyl phosphorothionates and dialkyl phosphates, ethyl phenylphosphonothionate and ethyl phenylphosphonate, pyrimidinediyl bis(diethyl phosphorothionates), and pyrimidinyl dimethylcarbamate were synthesized in the yields listed in Table 1. All the compounds synthesized and described in this paper gave appropriate spectral data for the assigned structures as shown in Table 1.

EXPERIMENTAL

General methods.

Pyrimidinols, pyrimidinediols, dimethylcarbamoyl chloride, dimethyl and diethyl phosphorothionochloridates, diethyl phosphorochloridates, diisopropyl and di-*n*-butyl hydrogen phosphites, phosphorus trichloride, and phenylphosphonothionodichloridate were obtained from commercial sources.

Several phosphorylating agents were prepared as follows: Diisopropyl and di-*n*-butyl phosphorochloridates were synthesized by introduction of Cl_2 gas into the corresponding phosphites benzene solution followed by de-chlorination with nitrogen gas babbling according to the previously reported method.[20]

Di-*n*-propyl phosphorochloridate was prepared by the same procedure as described above from di-*n*-propyl hydrogen phosphite synthesized by the reaction of phosphorus trichloride with *n*-propanol.

Ethyl phenylphosphonothionochloridate was prepared by the reaction of sodium ethylate with phenylphosphonothionodichloridate.

The phosphorylation of pyrimidinol and pyrimidinediol were monitored by thin-layer chromatography (tlc) using precoated silica gel

F_{254} chromatoplates (0.25 mm) and both view under ultraviolet (UV) light and selective spray reagents as follows: ammonium molybdate-perchloric acid for organophosphorus compounds; palladium chloride for sulfur-containing compounds; ninhydrin following alkaline hydrolysis for dimethylcarbamates. [7]

The products were purified by preparative tlc, or distillation until they gave a single tlc spot.

Preparative tlc utilized 1-mm-thick silica gel plates developed with appropriate solvent systems. The desired compounds were detected by uv visualization. The bands containing the desired compounds were scraped off the chromatoplates, extracted with a mixture of CH_2Cl_2 and Acetone (5 : 1) for 8 hr at room temperature (23°C). The extracts were filtered, and filtrates were evaporated *in vacuo*. Residual oils were dissolved in small amounts of CH_2Cl_2, collected into sample bottles, and evaporated by the nitrogen gas stream to give oils.

Solvent systems for analytical or preparative tlc used for these syntheses were as follows: A, CH_2Cl_2; B, CH_2Cl_2-Acetone (9:1); C, CH_2Cl_2-Acetone (10:1); D, CH_2Cl_2-Ethyl acetate-Acetone (12:3:1); E, Hexane-Acetone (7:2). Rf values of the products with the appropriate solvent systems are listed in Table 1.

Each compound was identified by chemical ionization/mass spectrometry (ci/ms) and by 90-MHz nuclear magnetic resonance (NMR) spectroscopy.

Chemical ionization mass spectra were obtained with isobutane as the reagent gas with a Finnigan Model 1015D mass spectrometer and NMR spectra were recorded with $CDCl_3$ solutions and tetramethylsilane (TMS) as the internal standard on a Perkin-Elmer R-32 spectrometer fitted with a Nicollet TT-7 Fourier transform computer.

Syntheses

*Substituted pyrimidinyl dialkyl phosphates, phosphorothionates, and ethyl phenyl-phosphonothionate. (Compounds **2**-**7**, **9** and **10**)*

Water was removed from a stirred mixture of pyrimidinol (5 mmol), K_2CO_3 (5.5 mmol), and benzene (15ml) by co-distillation on reducing the volume to 5 ml. Corresponding phosphorylating agent (**B**, **C**, **D**) (5 mmol) was then added and the mixture was allowed to stand with stirring at the temperature described in the Table 1, respectively. The residue following evaporation was dissolved in CH_2Cl_2 which was washed with ice water, dried (Na_2SO_4), and evaporated. Compounds were obtained as oils by preparative tlc with Rf values listed in Table 1. Yields of these compounds are also listed in Table 1.

*2-Ethyl-6-ethoxy-4-pyrimidinyl diethyl phosphorothionate (**14**)*

A mixture of 2-ethyl-6-ethoxy-4-pyrimidinol (2.5 mmol), K_2CO_3 (2.75 mmol), and acetonitril (5 ml) was heated at 40°C for 0.5 hr with stirring. Diethyl phosphorothionochloridate (2.5 mmol) was added to the mixture at 25°C and stirring was continued at 50°C for 3 hr. After workup as above, preparative tlc gave compound **14** as a liquid in 58% yield.

*Oxidation of thion (**1**) (**9** and etrimfos) by the use of MCPBA*

Oxons (**8** and **13**) were prepared by oxidizing phophorothionates **9** and etrimfos, respectively, with m-chloroperbenzoic acid[18] in CH_2Cl_2 washing the reaction mixture with 2% NaOH solution, and tlc purification.

*Substituted pyrimidinediyl bis(diethyl phosphorothionate) (**16**, **18**-**20**)*

Benzene was distilled off from a stirred mixture of pyrimidinediol (**E**) (5 mmol), K_2CO_3 (11 mmol), dimethylformamide (DMF) (5 ml), and benzene (25 ml). Diethyl phosphorothiono-chloridate (**F**) (10mmol) was added and the mixture was stirred at 65°C for 3 hr. Workup involved addition to 2% aqueous NaOH solution, extraction with CH_2Cl_2, washing the

CH_2Cl_2 layer with 2% NaOH solution and then with water, drying (Na_2SO_4), and evaporation. Compounds **16** and **18-20** were isolated by preparative tlc, as shown in Table 1.

Compound **17** was prepared by the same procedure except that benzene (20 ml) was used as the solvent and 10 ml of benzene was distilled off, the reaction was carried out at 70°C for 3.8 days.

*Carbonate (**21**).* A mixture of pyrimidinol (2.5 mmol) and finely powdered anhydrous K_2CO_3 (2.75 mmol) in dimethylformamide (DMF) (2 ml) was stirred at 40-50°C for 0.5 hr, then a equivalent of dimethylcarbamoyl chloride (**G**) in DMF (2 ml) was added and heated at 60°C with stirring for 1 hr. Product isolation involved addition of CH_2Cl_2, washing the mixture with water, drying (anhydrous Na_2SO_4) solvent evaporation and distillation to give 99% yield of compound **21**.

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